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(21) International Application Number: PCT/GB98/00068 (22) International Filing Date: 9 January 1998 (09.01.98) (30) Priority Data: 9700508.6 11 January 1997 (11.01.97) GB (71) Applicant (for all designated States except US): SMITH & NEPHEW PLC [GB/GB]; 2 Temple Place, Victoria Embankment, London WC2R 3BP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): SEARLE, Richard, John [GB/GB]; 12 Fairway Drive, Upper Poppleton, York YO2 6HE (GB). (74) Agent: SMITH & NEPHEW GROUP RESEARCH CENTRE; Group Patents & Trade Marks Dept., York Science Park, Heslington, York YO1 5DF (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: HYDROGELS (57) Abstract Cross-linked polyester hydrogels, suitable for use as medical implant devices or biodegradable supports for cell cultures used in for example cartilage repair, comprise residues of succinic acid and a polyol having at least three hydroxy groups.		

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HYDROGELS

The present invention relates to hydrogels. In particular, the present invention relates to polyester hydrogels.

5

Polyesters of succinic acid are known from US Patent No.3,883,901. Such polyesters are the reaction product of a succinate ester, such as diethyl succinate, and a glycol, such as polyethylene glycol.

10

Poly (1,4-butanediol succinate) is known from D K Song, Y K Sung, Journal of Applied Polymer Science, 56, 1381, (1995).

We have now surprisingly found that polyesters produced by reacting succinic anhydride with a polyol containing three or more hydroxy groups are novel and advantageous.

Thus, according to the invention we provide a polyester comprising residues of succinic acid and a polyol containing three or more hydroxy groups.

20

Thus according to a further feature of the invention we provide a water swellable hydrogel comprising a polyester which polyester comprises residues of succinic acid and a polyol containing three or more hydroxy groups.

25

By the term a water swellable hydrogel is meant a three-dimensional network of a super absorbent polymer which interacts with aqueous solutions by swelling and retains a significant proportion of water within its structure.

30

For the purpose of this invention a super absorbent polymer is understood to mean a polymer which is capable of having an equilibrium water content of at least 30% w/w.

35

We particularly provide a polyester as hereinbefore described with a number average molecular weight (M_n) of greater than

(4500), preferably greater than (10,000), and more preferably greater than (20,000).

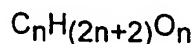
5 The high molecular weight polyesters of the invention are also advantageous over prior art polyesters in that they exhibit cross-linking.

10 Thus as a further feature of the invention we provide a cross-linked polyester of succinic anhydride and a polyol, eg. a cross-linked polyester comprising residues of succinic acid and a polyol containing three or more hydroxy groups. Such cross-linked copolyesters generally act as hydrogels.

15 Any conventional polyols containing three or more hydroxy groups known per se are suitable for use in the present invention. Such polyols include, for example, polyether polyols or polyhydroxyalkanes. It should be noted that the polyols for use in the present invention should not be limited to the polyether polyols or the polyhydroxyalkanes.

20

Polyhydroxyalkanes of the general formula



25 in which n is a number from 3 to 6,

are suitable for the preparation of the polyester of the invention and include, for example, glycerol, sorbitol, mannitol, adonite, ribite, dulcitol, erythritol and xylite. Polyols such as triols which may be
30 mentioned include trihydroxyalkanes such as glycerol.

Examples of polyether polyols include those sold under the range of TP30 by Perstorp.

35 It is also possible to use a mixture of polyols which will include mixtures of polyether polyols or mixtures of polyhydroxyalkanes. Especially preferred are mixtures of polyether polyols and polyhydroxyalkanes.

The polyesters of the invention may be prepared using conventional methods known per se.

5 Thus according to the invention we provide a method of manufacturing a polyester as hereinbefore described which comprises mixing succinic anhydride and a polyol containing three or more hydroxy groups and drying the mixture at elevated temperature.

10 The method of manufacturing a polyester according to the invention may optionally include the use of a catalyst. Preferred catalysts are acid catalysts and especially protic acid catalysts. Particular protic acid catalysts which may be mentioned include
15 sulphuric acid, methane sulphonic acid and p-toluene sulphonic acid.

 The ratios of the succinic anhydride and the polyol in the polymerisation reaction will depend upon, inter alia, the functionality
20 of the polyol, that is, the number of free hydroxy groups and the degree of cross-linking required in the resulting polyester. Thus if succinic anhydride has a functionality of 2, glycerol, which has two primary and one secondary hydroxy group is also considered to possess a functionality of 2 since the secondary hydroxy is less
25 reactive than the primary hydroxy groups. Defined in terms of functionality the ratio of succinic anhydride to polyol should be from 0.7:1 to 1:1.3, preferably 1:1. For example in molar terms a polyester of succinic anhydride and a triol such as glycerol should comprise preferably 3 units of succinic anhydride to 2 units of
30 glycerol, eg. giving a preferred functionality ratio of 1:1.

 Polyesters according to the invention may be characterised using conventional techniques known per se, such as infra red spectroscopy, nmr, rheological measurements, glass transition
35 measurements and water uptake.

 The polyesters according to the invention are particularly advantageous in that they are biodegradable. Thus they may be

useful in preparing biodegradable implants such as medical or surgical prostheses, supports for such prostheses, supports for cell cultures such as may be used in ligament, cartilage or tendon repair, supports for cell cultures in woundcare or as woundcare agents in
5 their own right, eg. debriding agents, pharmaceutical carriers etc. or the copolyesters of the invention may be useful in imaging during interventional procedures.

It is intended that the aforementioned uses should not be
10 limitative and are mentioned by way of example only.

The polyesters of the invention are also advantageous in that they are sterilisable. Any conventional form of sterilisation may be used, eg. steam sterilisation, but an especial benefit of the
15 polyesters of the invention is that they may be sterilised without detrimental effect by x-radiation.

Thus according to a further feature of the invention we provide a polyester as hereinbefore described in sterile form, eg. wherein
20 the sterilisation has been carried out by x-radiation.

Polyesters produced from succinic anhydride and diols are known in the prior art to be useful as bioresorbable sutures. Experimental results indicate that such polyesters, as well as the
25 polyesters of the present invention may be especially useful in wound healing, eg. as a debriding agent.

Thus according to the invention we provide the use of a polyester comprising residues of succinic anhydride and a polyol in
30 the manufacture of a wound healing agent, eg. a debriding agent.

According to a further feature of the invention we provide a method of wound healing which comprises applying a polyester comprising residues of succinic acid and a polyol to the wound of a
35 patient.

We especially provide the use of a polyester according to the invention as hereinbefore described.

The invention may will be illustrated but in no way limited by way of the following examples and by reference to the Accompanying drawings. Temperatures are stated in degrees
5 celsius.

Example 1

Preparation of Polyesters I

10 Aliquots of Polyol TP30 (from Perstorp) and succinic anhydride were mixed together in the ratios shown in Table 1 in a closed jar and heated on a hotplate for a few minutes, whilst stirring. A clear solution resulted. One drop of methanesulphonic acid (MSA) was added, and stirring continued for about a minute. Each solution was
15 poured onto the silicone side of a release paper, and placed in a petri dish in a desiccator containing succinic anhydride (3g) and a tray of dried silica gel.

The desiccator was heated in an oven at 80° for 5 to 15 mins
20 with the tap open. It was then heated with the tap closed for a further 15 to 16 hrs at 80°. The resulting materials were heated in a vacuum oven at 70°.

TABLE I

Reaction	Stoichiometry	Succinic anhydride/mmol	TP30
Number	COOH:OH*	(mmol COOH eq)	mmol OH
1	1:1.3	20 (40)	52
2	1:1.29	20 (40)	51.8
3	1:1	20 (40)	40.2
4	1:1	20 (40)	40.3

*Succinic acid is considered to have a COOH stoichiometry of 2.

5

Example 2

Swelling in Water

Several materials resulting from Reaction 1 of Example I
 10 (1:1.3/COOH:OH) were swollen in water. The weight change results after 1 day swelling are shown in Table II.

TABLE II

Time Under Vacuum	% Weight Gain
3h 40mins	33.3
7h 15mins	40.8

15

Example 3

Preparation of Polyesters II

Aliquots of Polyol TP30 and succinic anhydride in the ratios shown in Table III were mixed in a closed glass vessel and heated
 20 on an oil bath until a clear solution resulted. Methanesulphonic acid (MSA) was added, and stirring continued for about a minute. The solution was poured into a tray of dried silica gel. When the temperature had equilibrated to 80°, the oven valves were closed, except that one valve was left very slightly open to prevent pressure
 25 build-up in the event of thermostat failure. Vacuum was not applied. Products were removed from the oven after 16 hours.

TABLE III

<u>Reaction Number</u>	<u>No. Millimoles COOH</u>	<u>No. Millimoles OH</u>	<u>COOH/OH Ratio</u>	<u>% w/w MSA</u>
261/1a	19.48	19.49	1	0.56
261/1b	24.11	24.13	1	0.56
261/1c	31.23	31.25	1	0.56
261/3	164.67	163.62	1.01	0.35
261/6	73.09	72.04	1.01	0.66
261/7	55.91	55.59	1.01	0.5
261/8	77.87	77.12	1.01	0.58
261/11	77.33	76.69	1.01	0.78
261/12	59.39	58.62	1.01	0.51

5

A second series of materials were prepared containing various levels of glycerol and TP30. The formulations are shown in Table IV.

TABLE IV

Reaction No.	Glycerol (mmol primary OH)	TP30 (mmol OH)	Succinic Anhydride (mmol COOH eq)	% Glycerol (mol primary OH)	COOH/OH ratio
261/9	8.07	69.94	78.14	10.3	1.00
261/10	16.20	62.71	78.24	20.5	0.99
261/13	23.73	23.93	47.71	49.8	1.00
261/14	127.92	42.37	170.55	75.1	1.00
261/16	220.37	220.83	439.99	49.9	1.00
261/17	252.20	249.80	499.65	50.2	1
261/18	249.39	249.58	500.84	50.0	1
261/19	213.31	212.82	427.52	50.1	1
261/20	227.48	221.04	442.45	50.7	0.99

5 Table V shows the degrees of conversion $p(\text{COOH})$ for these materials, calculated using the method shown below.

Degree of conversion was estimated from the weight loss, ie. water loss, during the reaction using Equation (1) below.

10 Water loss from the reaction is derived from the following sources:

- a) water present in the polyol
- b) water liberated in the reaction
- 15 c) water present in the anhydride
- d) water absorbed from the atmosphere.

c) is assumed to be negligible since the anhydride is stored under nitrogen, though any water absorbed would convert the anhydride to succinic acid and would therefore manifest itself as an error in b). This water would in fact be liberated during the reaction.

20 d) is assumed to be negligible since the reaction is carried out in a

sealed system in the presence of a drying agent, followed by vacuum treatment.

5 a) was calculated from the measured water content of the polyols.

b) was calculated from the amounts of materials used in the reaction. Since each mole of anhydride gives rise to one mole of water (Figure 1), the total mass of water expected in the reaction m_w is given by

10

$$m_w = m_a m_T \times 18$$

$$\frac{M_a m_T}{M_a m_T}$$

15

where

m_a is the mass of the anhydride in the mixture (during the initial mixing procedure)

20

m_T is the total mass of mixture initially prepared

m_T is the total mass of mixture poured onto the release paper

25

M_a is the molecular mass of succinic anhydride.

TABLE V

Reaction	COOH/OH Ratio	Scale/g	% Glycerol (mol primary OH)	p(COOH)
261/9	1.00	13.8	10.3	46.7
261/10	0.99	13.4	20.5	80
261/13	1.00	12.0	49.8	92
261/14	1.00	21.5	75.1	not calculated
261/16	1.00	60.0	49.9	68.4
261/19	1.00	59.8	50.1	68.3

Example 55 Swelling Measurementsa) 0% Glycerol

Figure 1 shows the percentage weight gain of the materials prepared without glycerol in both deionised water and phosphate buffered saline (PBS) as a function of time (batch number PC0695042, from Reaction 261/12, Table III).

b) 50% Glycerol

Figure 2 shows the percentage weight gain of the materials with 50% glycerol (based on mol % primary OH) in both deionised water and PBS as a function of time (batch number PC0695041, from Reaction 261/13, Table IV).

c) 75% Glycerol

Figure 3 shows the percentage weight gain of the materials with 75% glycerol (based on mol % primary OH) in both deionised water and PBS as a function of time (Reaction 261/14, Table IV).

Example 6FTIR Spectroscopy

5 Figures 4 and 5 are FTIR spectrographs of two polyesters of
the invention. In each case the spectra showed bands characteristic
of polyesters, such as ester carbonyl at 1720cm^{-1} and C=O
stretching around 1300cm^{-1} , together with ether C-O stretching from
the ethoxylated polyol at 1100cm^{-1} . Figure 4 shows the FTIR
spectra of the polyester produced from reaction 261/7 from Example
10 3 (Table IV) and Figure 5 shows that of the reaction product from
Reaction 261/10 of Example 3 (Table V).

CLAIMS

1. A hydrogel composition comprising a cross-linked polyester containing residues of succinic acid and at least one polyol having at least three hydrogel groups, said composition being adapted to absorb at least 30% of its weight of water.
2. A composition according to claim 1 having an average molecular weight (M_n) of greater than 4500.
3. A composition according to claim 1 or claim 2 wherein the polyol is a polyester polyol, a polyhydroxy alkane or a mixture thereof.
4. A composition according to any one of the preceding claims wherein the polyester is the product of reaction between succinic anhydride and a polyol.
5. A composition according to claim 4 wherein the functionality ratio between succinic anhydride and said polyol is from 0.7:1 to 1:1.3.
6. A polyester comprising residues derived from succinic anhydrides and at least one polyol having at least 3 hydroxyl groups.
7. A medical device formed for a composition as claimed in any one of claims 1 to 6.

FIG. 1. 1/3

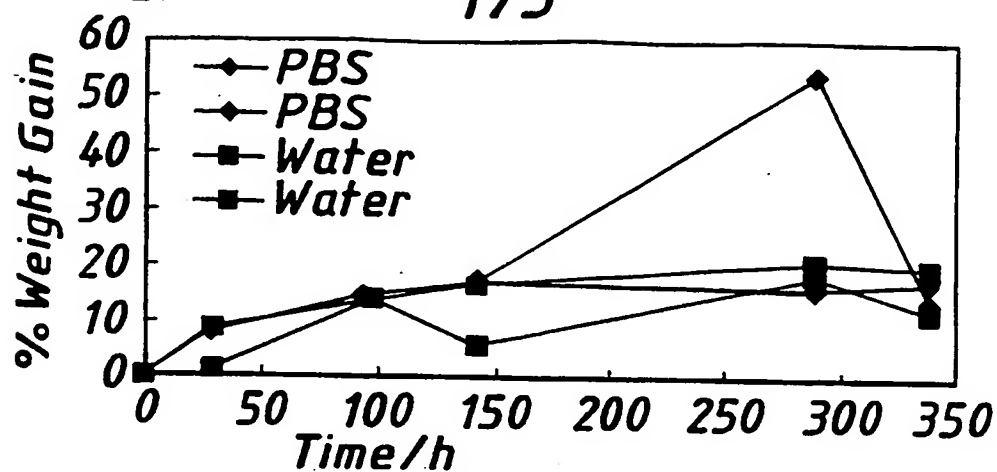


FIG. 2.

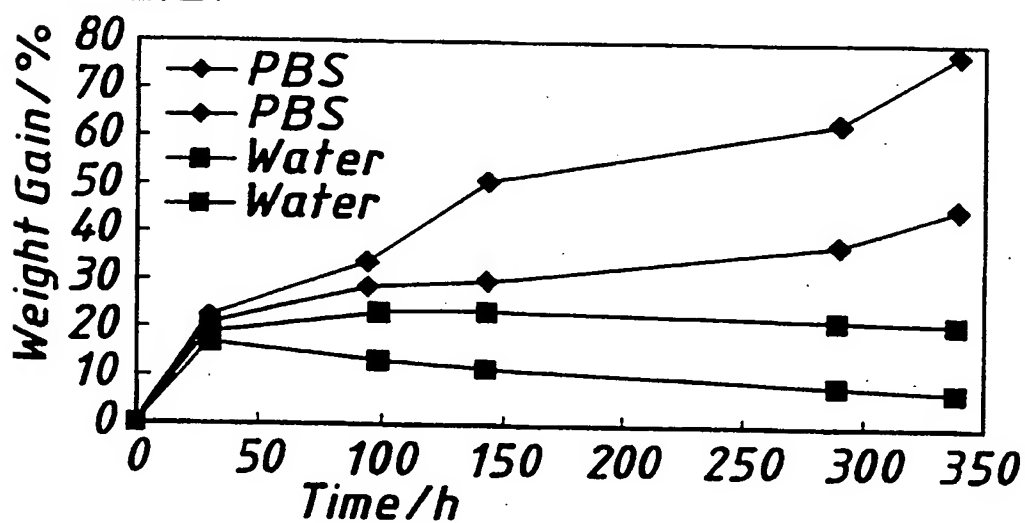
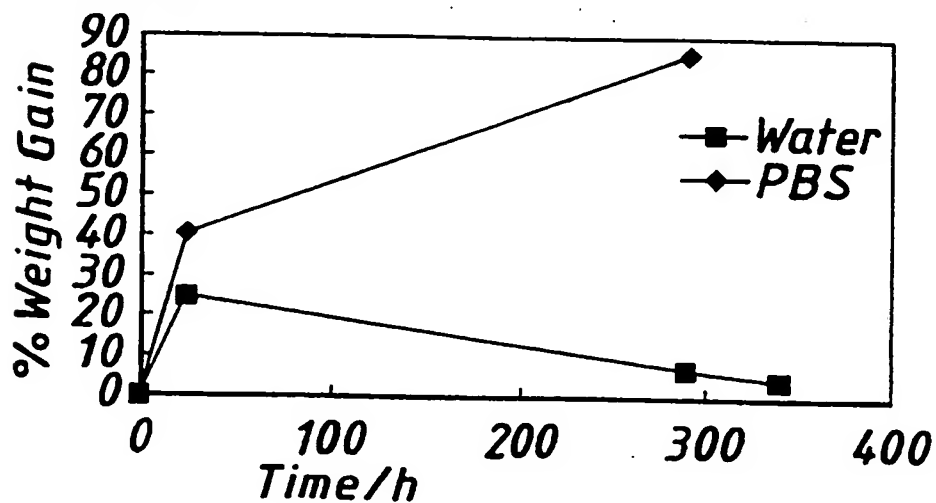
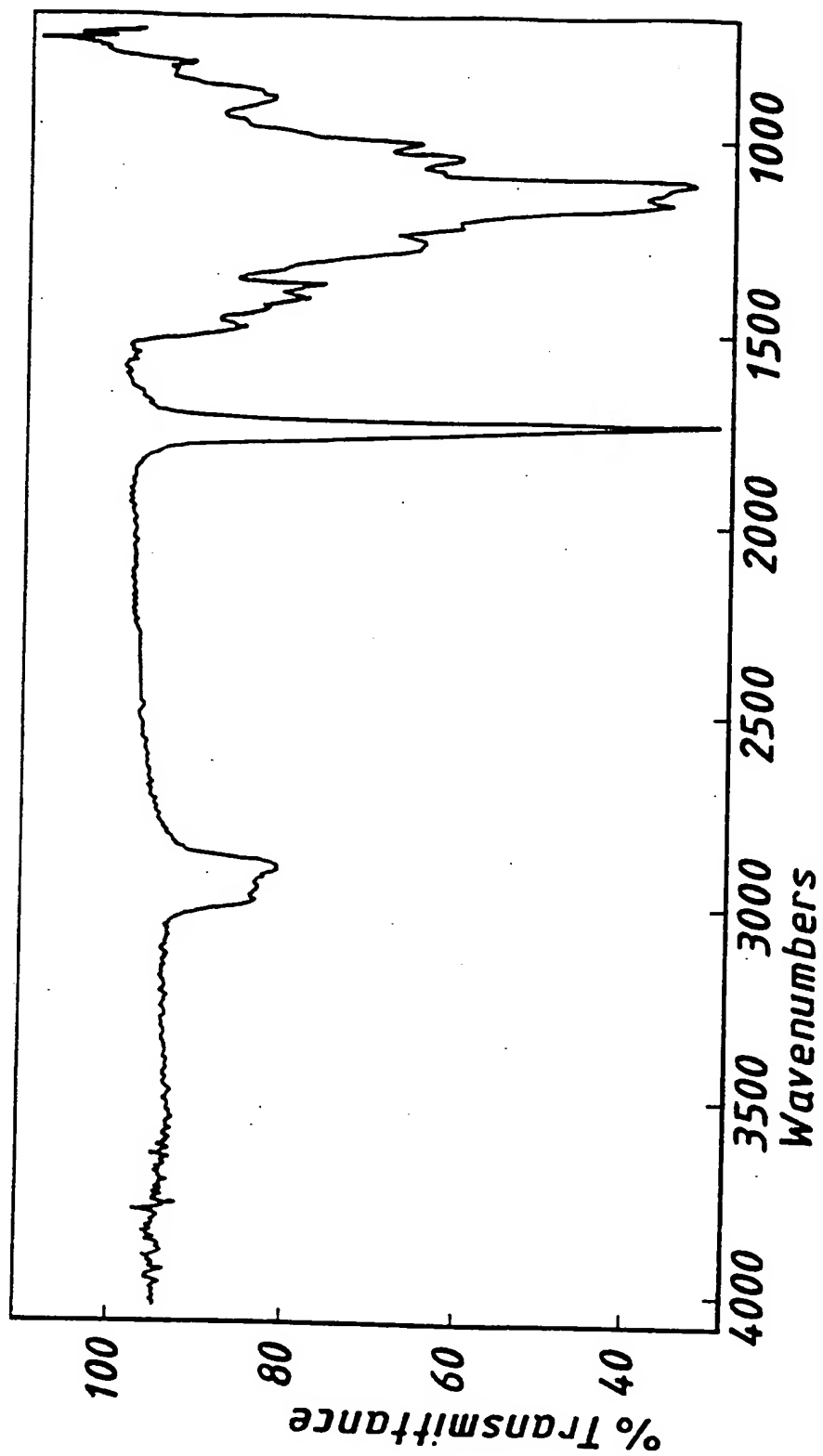


FIG. 3.



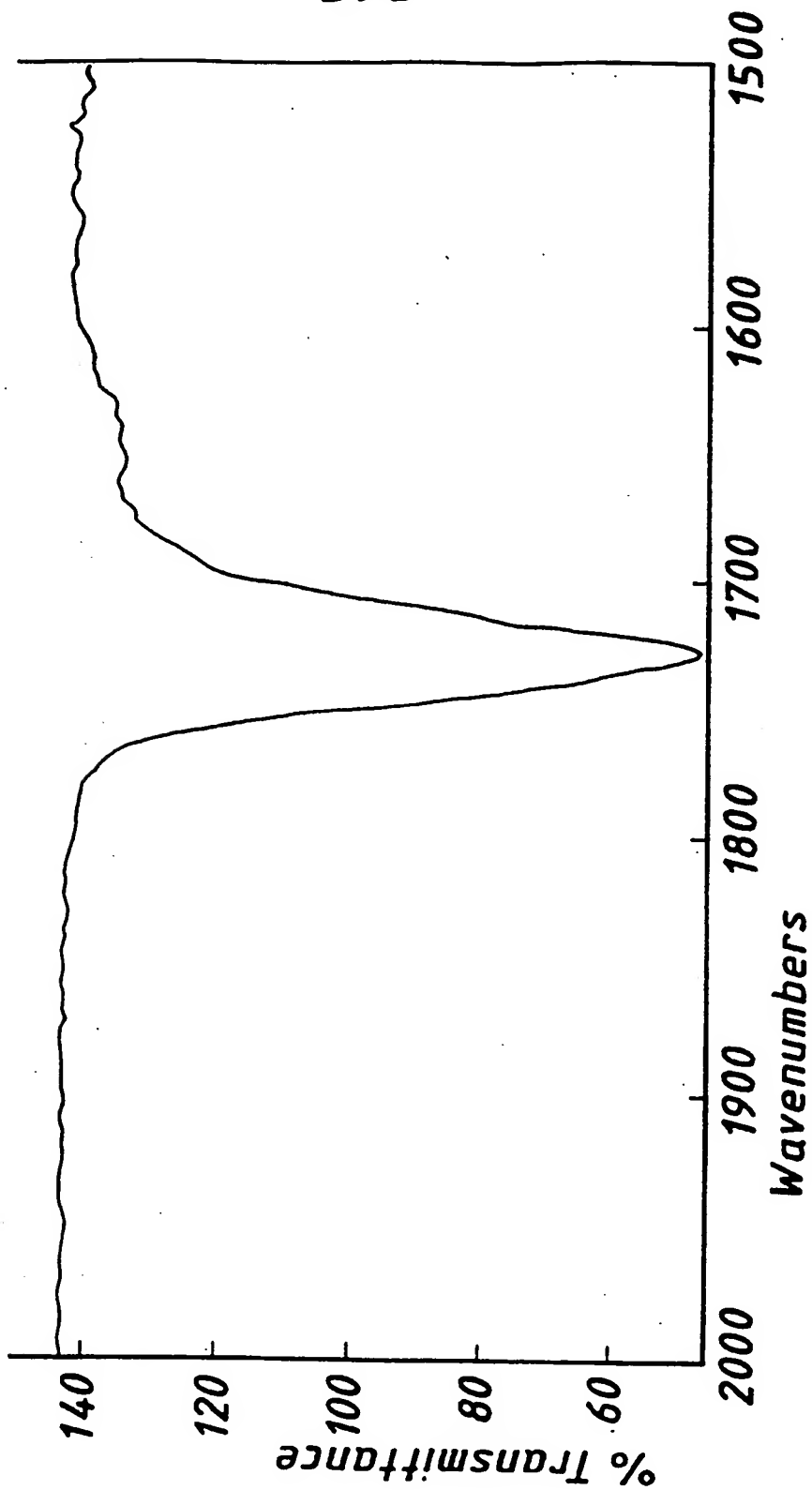
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FIG. 4.



3/3

FIG. 5.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00068

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C08G63/12 C08G63/668 A61L31/00 A61L27/00 A61L25/00
A61L15/60

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C08G A61L

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 104, no. 12, 24 March 1986 Columbus, Ohio, US; abstract no. 95260, HIGAKI ET AL.: "Novel, hydrophilic polyol esters for hair preparations" XP002061206 see abstract & JP 60 031 802 B (NISSHIN OIL MILLS LTD) 24 July 1985 --- -/--	1-6

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	<p>CHEN ET AL.: "Enzymatic and chemoenzymatic approaches to synthesis of sugar-based polymer and hydrogels" CARBOHYDRATE POLYMERS., vol. 28, no. 1, 1995, BARKING GB, pages 15-21, XP000539360 see page 17, left-hand column, line 26 - right-hand column, line 55</p> <p>-----</p>	1-7